

Original Article

The predictive value of neutrophil-to-lymphocyte ratio to diagnose acute appendicitis and grade its severity

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ABSTRACT

Background: Acute appendicitis (AA) is one of the most common acute abdominal emergencies in the pediatric population, occurring commonly between the ages of 7-15 years. The diagnosis mostly depends upon typical presentation and clinical findings. Laboratory investigations and imaging techniques aid the diagnosis. Neutrophil to lymphocyte ratio (NLR) is a valuable indicator of diagnosis in questionable cases.

Methods: This is a retrospective study consisting of 260 pediatric patients who underwent appendectomy. The study was conducted at the Department of Pediatric Surgery, Maternity and Children's Hospital Dammam, Saudi Arabia. The duration of the study was May 2018 to March 2021. The clinical features and initial preoperative total leukocyte count (TLC), with neutrophil and lymphocyte values, were collected. The neutrophil to lymphocyte ratio (NLR) was preoperatively calculated by dividing the values obtained. The patients were categorized in group 1 as non-appendicitis and group 2 as appendicitis. On the basis of histopathological findings, group 2 was further divided into catarrhal, phlegmonous, and gangrenous/perforated as groups A, B, and C respectively. The value of NLR was compared between the groups.

Results: The children with acute appendicitis had a higher NLR than healthy children. Acute appendicitis was ruled out at 2 cut-off-value of NLR with 94% sensitivity and 100% specificity. An NLR of 3.5 was an accurate marker for acute appendicitis. Significant differences in NLR values were also observed in the severity of appendicitis. Phlegmonous appendicitis had 78% sensitivity and 82% specificity at a cut-off value of 6.0 while NLR of > 8.0 was the cut-off point for gangrenous/perforated appendicitis with 80 % sensitivity and 87% specificity.

Conclusion: The NLR is a reliable biomarker to exclude, diagnose, and grade the severity of acute appendicitis. It is a valuable indicator of atypically presented cases or cases lacking adequate clinical findings. The yield of the test is increased in conjunction with other laboratory parameters.

Keywords: Acute appendicitis, Children, Diagnosis, Neutrophil/lymphocyte ratio, Severity.

INTRODUCTION

Acute appendicitis (AA) is one of the most common causes of abdominal pain in children. It is common between the ages of 7-15 years but can occur at any age. It occurs less frequently under five years of age¹ because there is a temporal relation between the incidence of appendicitis and the development of submucosal lymphoid follicles at and near the base of the appendix. These collections of reactive immune cells are sparse at birth but increase with age to peak in adolescents, making the appendix susceptible to obstruction and

inflammation.^{2,3} A lifetime risk of appendicitis has been estimated at 8.7% for boys and 6.7% for girls.³ Despite advances in medical research in the field of laboratory and radiological modalities, diagnosis of AA is still based on history and physical examination.⁴

The AA is the most common misdiagnosed surgical cause of acute abdomen in children.^{5,6} The delay in diagnosis or misdiagnosis is attributed to non-specific symptoms, overlapping of symptoms with other illnesses, child's inability to explain, and the difficult abdominal examination in this age group. Moreover, variation in the

location of the appendix such as hidden or retrocaecal appendicitis, may not exhibit enough signs to support diagnosis. The delay in diagnosis of AA is associated with increased risk of gangrene, perforation, intra-abdominal abscess formation, peritonitis, sepsis, and ileus,^{7,8} and misdiagnosis leads to negative appendectomy. A certain rate of negative explorations for suspected appendicitis, especially in girls, is acceptable because of the devastating impact of perforated appendicitis.⁹ Negative pathology results can be seen in 10-30% of the patients operated on in spite of using ultrasound (US) and computerized tomography (CT) as diagnostic tools.

Laboratory findings could help in diagnosis, but misinterpretation of laboratory values is still common.¹⁰ Complete blood count (CBC) is the first line of laboratory evaluation to diagnose appendicitis.⁴ It is an inevitable and easily found baseline hematological parameter in the laboratories. A rise in leukocyte count is the most frequent finding.¹⁰ But the accuracy of WBC and neutrophil for diagnosis of acute appendicitis varies among studies.² Moreover, normal leukocyte counts do not exclude appendicitis.¹ Another laboratory predictor, C- reactive protein is a sensitive test but is nonspecific for acute appendicitis.¹⁴ Although laboratory tests are useful biomarkers in inflammatory conditions but no single test predicts accurately the diagnosis of acute appendicitis, especially in the early stage.^{2,4} Abdominal ultrasound can be helpful in diagnosis but it is operator dependent, and also the presence of gas in the bowel and obesity, are challenges to the diagnosis.¹² The computed tomography has high accuracy to diagnose an AA, but it is relatively expensive, with limited availability and high radiation risk.²

Studies have been conducted for a prompt and correct diagnosis to avoid complications resulting from late diagnosis and also to avoid negative explorations. A number of other inflammatory markers have long been proposed as tools to support the clinical data in decision-making process to determine AA.^{6,7} It has been reported that neutrophil/leukocyte ratio (NLR) is a good predictor in preoperative diagnosis of AA.^{5,13} Neutrophils have a pivot role in the immune system. These are regarded as a powerful component in fighting infection, that is why infectious diseases caused by bacteria show NLR changes. There are numerous studies indicating that NLR is a valuable indicator in the differential diagnosis of appendicitis compared to healthy volunteers when it is above 3.5.^{1,14} Some other authors had reported that NLR may also help to distinguish complicated from non-complicated appendicitis.⁶ The NLR is a novel inflammatory marker and the value of NLR rests on its readily available nature, calculated from blood count, inexpensive and easily applicable investigation to diagnose AA without losing time. The aim of the study is to analyze the

contribution of the NLR level to predict acute appendicitis and to distinguish the severity of appendicitis.

METHODS

This is a retrospective study of 260 pediatric patients who underwent appendectomy and had histopathological findings consistent with acute appendicitis (AA). This study was conducted at Maternity and Children's hospital Dammam, Saudi Arabia and the duration of the study was from May 2018 to March 2021.

The study population was separated into 2 groups. The 1 group consisted of 260 children, who were otherwise healthy, but operated on for non-inflammatory pathologies such as inguinal hernia, undescended testes, and umbilical hernia. Group 2 comprised 260 appendicitis cases which were further divided into group A as simple/catatrrhal or endo-appendicitis (SA), group B having uncomplicated appendicitis (UA), or phlegmonous appendicitis, and group C composed of gangrenous/perforated appendicitis noticed as complicated appendicitis (Table-1).

Table 1: Division of appendicitis into three groups

Types of appendicitis	No. of cases	Percentage
Simple appendicitis (Group – A)	50	19.23
Phlegmonous appendicitis (Group – B)	170	65.38
Gangrene/perforated appendicitis (Group – C)	40	15.38

The inclusion criterion was pediatric patients of age < 14 years, presented with abdominal pain, diagnosed with appendicitis, and underwent appendectomy. The patients admitted with abdominal pain due to other reasons such as cystitis, pyelonephritis, gastroenteritis, mesenteric adenitis, Henoch-Schonlein purpura, abdominal trauma, and patients with the incomplete medical records, were excluded from the study.

All data were collected retrospectively from hospital database records. For each patient, the age, sex, presenting symptoms, laboratory values, and operative findings were recorded. The clinical diagnosis was based on history (abdominal pain, vomiting, and fever), physical examination (tenderness at McBurney's point), traditional laboratory tests (TLC, DLC), and in some cases imaging studies, were performed. Preoperative informed written consent was obtained. The pathological diagnosis was determined by intraoperative findings combined with histopathological findings of the resected appendix. Total Leukocyte count with a differential count of neutrophils and lymphocytes were recorded at the time of first evaluation. The analysis was done by an automated cell counter. The NLR value was obtained by dividing absolute neutrophil count by absolute

lymphocyte count. The study protocol was approved by the Institutional Review Board.

RESULTS

This study enrolled a total of 260 cases that underwent appendectomy compared with 260 healthy patients. The median age of the study group was 9 years (range; 2-14 years). In all, 170 (65.38%) were male and 90 (34.61%) were female.

About 50% of patients fall between 8-12 years of age (Table-2). All the operated patients had histopathologically proven appendicitis. Simple appendicitis (group A) was found in 50 (19.23%) patients while phlegmonous appendicitis (group B) consisted of 170 patients (65.38%).

Table 2: Age distribution

Age	No. of cases	Percentage
0-2	1	0.38
2-4	12	4.62
4-6	33	12.70
6-8	47	18.07
8-10	71	27.30
10-12	63	24.23
12-14	33	12.70
Total	260	100

The gangrenous/perforated appendicitis (group C) was composed of 40 patients (15.38%). Table-1. The control group (Group 1) had an NLR range of 0.97- 1.92 with an average of 1.45 ± 0.48 , while the appendicitis group (Group 2) had an NLR of 1.50-26.37 with an average of 13.93 ± 12.43 . All patients of group 1 had NLR less than 2, while Group 2 patients having NLR greater than 2 comprised 246 cases with 94% sensitivity and 100% specificity (Table-3).

Table 3: Comparison of sensitivity and specificity of groups at specific cut-off point

Group	N/L ration	Cut-off point	Sensitivity	Specificity
Group-1	0.97-1.92 (1.45 ± 0.48)	>2.0	94%	100%
Group-2	1.50–26.37 (13.93 ± 12.43)			
A	1.50-7.92 (4.71 ± 3.21)	3.5	79%	65%
B	3.50-26.37 (14.93 ± 11.43)	6.0	78%	82%
C	2.75-23.45 (13.10 ± 10.35)	≥ 8.0	80%	87%

Group-A had an NLR range of 1.50-7.92 with an average of 4.71 ± 3.21 . The highest sensitivity and specificity for the NLR for simple appendicitis were 79% and 65% respectively at a cut-off value of 3.5. The NLR in group B and groupmC was 3.5-26.37 and 2.75-23.45 with an average of 14.93 ± 11.43 and 13.10 ± 10.35 , respectively.

Utilizing an NLR of 6.0 as a predictor of phlegmonous appendicitis, the cut-off point had a sensitivity of 78% and specificity of 82%. A significant association was observed for gangrenous/perforated appendicitis at NLR of > 8.0 with 80% sensitivity and 87% specificity.

DISCUSSION

The main aim of a surgeon should be to make an accurate and prompt diagnosis to avoid complications owing to delay in diagnosis 15,16,17 and also to prevent unnecessary surgery. Although complete clinical judgment, laboratory findings, and imaging modalities are usually necessary to make the diagnosis, all these have limitations. So, in this regard, a search for some other diagnostic parameters was necessary. Goodman et al. have searched for a diagnostic criterion using the NLR and they compared the relationship between neutrophil and lymphocyte counts and reported that an NLR higher than 3.5 was a sensitive predictor of appendicitis.5 Similarly Yazici in 2010 found in his study that an NLR score greater than 3.5 is a more accurate as a predictor factor when compared with total leukocytes.7,10,13

The rationale for NLR as a potent indicator depends upon the inflammatory process. We know that Inflammation is the vascularized response of living tissue to foreign insult, consisting of a change in blood flow, increased neutrophils count in the bloodstream, and migration of cells from the bloodstream to the injured tissue7. Although the pathophysiological mechanism of lymphopenia is not known completely, the direct effect of toxins or glucocorticoid cytokines, and other mediators or sequestration in inflammatory phlegmon was suggested as the reasons.5 So, any systemic inflammatory response can cause neutrophilia and lymphocytopenia, resulting in an increase in the NLR, a sign of inflammation in AA.7,13,17 This finding may be particularly important when clinical findings and WBC are not adequate to make a safe diagnosis of AA.7

Our study showed that appendicitis was ruled with NLR at a cut-off value of 2.00 because all patients in the non-appendicitis group (group-1) revealed NLR less than 2.0. So, NLR has not only a predictor value but it seems to have a role in the exclusion of appendicitis. Similarly, in our study, the NLR of 3.50 with 79% sensitivity and 65% specificity seems to be the most useful cut-off value in the diagnosis of catarrhal appendicitis (group-A). Our result is in agreement with the findings of Sevin et al who found the optimal cut-off value of 3.5 with 76.6% sensitivity and 59.3% specificity.6 In another study done by Bialas et al, determined an NLR cut-off value of 3.5

with 77.5% and specificity of 73.3%.^{6,18} Some other studies have also shown NLR of 3.5 is a useful factor to diagnose catarrhal appendicitis and distinguishing it from complicated appendicitis.^{5,7,17} Similarly, Kostakis ID, et al have found NLR >2.5 an accurate marker for acute appendicitis in children.¹⁹ In literature a higher cut-off value of 6.05 is also documented.^{9,13} Comparing phlegmonous appendicitis (group-B) with catarrhal appendicitis (group-A), phlegmonous appendicitis has a sensitivity of 78% and specificity of 82% at a 6.0 cut-off value of NLR. The cut-off value of NLR distinguishing the catarrhal and phlegmonous appendicitis may be a good clinical indicator for the introduction of antibiotics. In our study, this cut-off value was comparable with a value determined by Kapetanovic SB, where sensitivity was 79% and specificity was 81% at a cut-off NLR of > 5.61.⁶ A significant association was observed for gangrene/perforated appendicitis at NLR of >8.0 which has 80% sensitivity and 78% specificity. This finding is in accordance with one other study revealing NLR >8.8 with 76.91% sensitivity and 100% specificity, as an independent predictor of complicated appendicitis.⁶ Moreover, this value is quite compatible with a study by Ishizuka et al, which also showed a cut-off-value of 8.0 for gangrenous/perforated appendicitis.⁷

We found that NLR was significantly higher in the acute appendicitis group than the non-appendicitis group, indicating a useful parameter to avoid unnecessary surgical operations. Our study also revealed that NLR is

a potent factor to differentiate the severity of appendicitis.

CONCLUSION

Our study suggests that NLR is a simple, not expensive, readily available, and affordable biomarker. It is important not only to exclude, predict, diagnose and prevent complications of appendicitis but also to avoid negative laparotomies, particularly when there is atypical presentation, inadequate clinical findings, and no other laboratory variables are available which can be used to concrete the diagnosis in the emergency department. At the same time, the value of NLR is enhanced when it is considered as an adjunct to other clinical and laboratory parameters.

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